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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NICHOLS, CHRISTOPHER J	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/054,873	GAN, ZHONG-RU	
	Examiner	Art Unit	
	Christopher J. Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *98-104,109-111,114-124,129-131 and 134-144* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *98-104,109-111,114-124,129-131 and 134-144* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *See Continuation Sheet* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims subject to restriction and/or election requirement are 98-104,109-111,114-124,129-131 and 134-144.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The Response and Amendment filed 19 January 2005 has been received and entered in full.

2. Prosecution on the merits is hereby *reopened* to allow entry of new rejections.

New Objections

Specification

3. The disclosure is objected to because of the following informalities: the Table of Contents contains page numbers. These will not match the mature patent or the patent application publication. Applicant should remove to avoid printing errors. Appropriate correction is required.

Claim Objections

4. Claims **98-104, 109-111, 114-115, 119-124, 129-131, 134-135, 138-140,** and **143-144** are objected to because of the following informalities: the term "peptidyl" is unclear. The Examiner takes it to mean "peptide". Appropriate spelling correction is required.

New Rejections

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims **98-104, 109-111, 114-124, 129-131,** and **134-144** are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. "A nucleic acid" is a product of nature and therefore non-statutory subject matter. The Examiner respectfully suggests use of art-accepted terminology to differentiate the instant nucleic acid from natural ones such as "isolated" or "recombinant".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims **98-104, 109-111, 114-124, 129-131,** and **134-144** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *an isolated nucleic acid encoding a chimeric protein, wherein said chimeric protein comprising the amino acid sequence SEQ ID NO: 6 or SEQ ID NO: 7,*

does not reasonably provide enablement for *peptidyl fragments, bioactive conformation, or other unspecified variants thereof.* The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

6. The claims are drawn very broadly to any nucleic acid which comprises two parts. The first part only required to be have "sufficient" homology to human growth hormone (hGH) and the second to comprise a human insulin precursor. The language of said claims encompasses a large number of proteins of 20 amino acids and longer, which are not required by the claim language to have any specific activity. The insulin precursor encompasses preproinsluin, proinsulin, and unfolded insulin so long as it is human. The insulin precursor does not require any specific structure or function to be retained (instant Specification pp. 24 lines 12-22).

7. The specification teaches that hGH can be used as a covalently linked intramolecular chaperone to improve the folding efficiency of human insulin in an *E. coli* system (Example 5 pp.23-26).

8. The specification fails to provide any guidance for the successful isolation and use of any hGH intramolecular chaperone shorter than 20 amino acids or longer than 92 amino acids. And since resolution of the various complications in regards to targeting the role a new function of a protein is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of formulations of hGH as an intramolecular chaperone and a large number of sequences related by homology. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

9. Additionally, a person skilled in the art would recognize that predicting the efficacy of using hGH related proteins as intramolecular chaperones based solely on the performance of a single species and such a small fragment of the protein as highly problematic (see MPEP §2164.02). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed nucleic acid, such a disclosure would not be considered enabling since the state of protein biochemistry is highly unpredictable and complex. The factors listed below have been considered in the analysis of enablement [see MPEP §2164.01(a) and *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)]:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

10. The following references are cited herein to illustrate the state of the art of intramolecular chaperones and protein biochemistry.

11. On the breadth of the claims, the art teaches that an exogenous peptide can be used as an activating peptide to improve the folding of a target polypeptide when the activating peptide has the amino acid sequence of the prosequence of the target polypeptide or of a polypeptide which has the same function as the target polypeptide and which is similar in amino acid sequence to the target polypeptide. US 5719021 (**IDS**) discloses use of this method for target polypeptides such as carboxypeptidase A, carboxypeptidase B, leucine aminopeptidase, N-terminal exopeptidases, pepsin, chymotrypsinogen, thrombin, prothrombin, pancreatic elastase,

cathepsins, kinin-forming and kinin destroying enzymes, streptococcal proteinase, collagenases, colstripain, and renin (claims 1-23).

12. On the nature of the invention, while general guidance is given regarding the use of human growth hormone (hGH) as the intramolecular chaperone for SEQ ID NO's 6 and 7 insufficient species examples are presented for the full genus of sequence variants, mutations, derivatives, and fragments with the desired bioactivity as an intramolecular chaperone. The art recognizes that sequence identity is not a reliable indicator of structure and function. Due to the large quantity of experimentation necessary to identify all the applicable sequences, the lack of direction/guidance presented in the specification regarding synthesizing, screening, and evaluating all applicable sequences, the absence of working examples directed to known sequences that have "sufficient amino acid sequence homology to at least a first 20 N-terminal amino acids of human growth hormone".

13. On the state of the prior art, Inouye (1991) "Intramolecular Chaperone: The Role of the Pro-Peptide in Protein Folding." Enzyme **45**: 314-321 (**IDS**) teaches the mutations in the pro-peptide form of subtilisin can eliminates its activity as an intramolecular chaperone (IMC). For instance, deletion of the first 14 or 43 residues on the N-terminus of pro-subtilisin eliminated its ability to function as an IMC for subtilisin (pp. 315). Also, synthetic subtilisin pro-peptides corresponding to –44 to –77, -1 to –64, and –1 to –43 are incapable of binding subtilisin and thus can not act as IMC's (pp. 316). Also, point mutations in pro- subtilisin like Gly to Arg at position –76, Met to Thr at position –60, Lys to Glu at position –45, Asp to Asn at position 32, Val to Ala at –13 eliminate the IMC activity of pro-subtilisin (pp. 316-317; Figure 1).

14. On the level of predictability in the art, the claims which fail to recite limitations for what constitutes an applicable sequence that has "sufficient" homology an unspecified sequence of hGH, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

15. On the existence of working examples, as noted by the Applicant in the specification, the results from the above experiment were unexpected (pp. 2, 9-10). Thus, neither the art nor the specification gives support for use of an intramolecular chaperone other than SEQ ID NO: 1 and SEQ ID NO: 2.

16. Regarding derivatives and fragments of hGH and insulin precursor polypeptides, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 433-506]. However, Applicant has provided little or

no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400 (**IDS**); Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2 (**IDS**); Doerks *et al.* (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250 (**IDS**); Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223 (**IDS**); Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133 (**IDS**); Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427(**IDS**)]. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and

possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

17. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *two species examples* and suggestion to the full range of chimeric proteins encoded by the nucleic acid instantly claimed as exemplified in the references herein.

18. Claims **98-104, 109-111, 114-124, 129-131,** and **134-144** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

19. The claims are drawn to a chimeric peptidyl fragment having "sufficient amino acid sequence homology" to a large genus of proteins (no particular disclosed sequence). The claims do not require that the polypeptide possess any particular conserved structure, or other distinguishing feature, such as a specific biological activity. Thus, the claims are drawn to a genus of polypeptides that is defined by sequence identity to an unspecific sequence.

20. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a partial structure in the form of a recitation of "sufficient amino acid sequence homology". The only species which are adequately described are SEQ ID NO: 6 and SEQ ID NO: 7. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. The only adequately described species for the two peptidyl fragments are: (a) human growth hormone and (b) human insulin precursor protein comprising the A chain and the B chain of human insulin. No active variants are disclosed. Accordingly, the specification does not provide adequate written description of the claimed genus.

21. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method

of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

22. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

23. Therefore, only isolated polypeptides comprising two peptidyl fragments: (a) human growth hormone and (b) human insulin precursor protein comprising the A chain and the B chain of human insulin but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

24. Claim **98** is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

25. Claim 98 recites the limitation "the bioactive conformation" in line 8. There is insufficient antecedent basis for this limitation in the claim.

26. Claim **98** is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

27. The limitation in claim 98 of "bioactive conformation" does not have any art accepted term nor does the Specification provide sufficient guidance as to the metes and bounds of this term.

Summary

28. No claims are allowed.

29. The Examiner notes that "human growth hormone" is also known as "somatotropin" (The American Heritage Dictionary of the English Language (2000) 4th Ed.)

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback** can be reached on **(571) 272-0961**.

The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

CJN
April 25, 2005

SHARON TURNER, PH.D.
PRIMARY EXAMINER
4-27-05